〒One-pot〒 synthesis of (-)-oseltamivir, 〒three-pot〒 synthesis of spirooxyindole alkaloids, and mechanistic investigation of organocatalyzed Michael addition of aldehydes into nitroalkenes

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論　文　内　容　要　旨

氏　　名	向山　貴祐	提出年	平成 26　年
学位論文の 題　　目	”One-pot” synthesis of (–)-Oseltamivir, “three-pot” synthesis of spirooxyindole alkaloids, and mechanistic investigation of organocatalyzed Michael addition of aldehydes into nitroalkenes （有機分子触媒を用いる不斉マイケル反応を利用したオセルタミビルの 1 ポット合成及びスピロオキシインドールアルカロイド類の 3 ポット合成）		

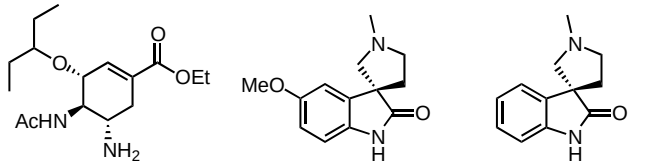
Contents

Chapter 1 Introduction

The development of environmentally benign synthetic methods is a current key topic in chemistry. When synthesizing molecules we need to consider both efficiency and sustainability, as indicated by terminology such as atom economy,[1] and step economy.[2] In addition to these terminologies, our group proposed "pot economy".[3] The synthetic method to conduct several transformations in a single vessel is called "one-pot" reaction. Since several transformations and bond formations can be achieved in a single vessel, it cuts several purification operations, and minimizes chemical wastes, enabling a shorter total production time. Thus, a "one-pot" reaction can also be regarded as environmentally benign, and "pot economy" should be considered when planning a synthesis. The "one-pot" reaction has a potential to reduce a number of reaction steps, enabling the synthesis of complex molecules easier compared with previous way.

On the other hand, the field of organocatalyst is rapidly growing since List, Barbas III and Lerner have discovered the intermolecular aldol reaction of acetone with aldehydes, catalyzed by proline.[4] The organocatalyst is regarded as an environmentally benign as it is constituted by elements such as carbon, nitrogen, hydrogen, sulfur, and so on, not including any toxic heavy metal. Our group has developed diphenylprolinol silyl ether as an organocatalyst, which catalyzes asymmetric Michael reactions to produce chiral molecules.[5]

In this doctoral thesis, I aimed to develop an efficient synthetic method of (–)-Oseltamivir (**1**), (–)-Horsfiline (**2**), and (–)-Coerulescine (**3**), which possess interesting biological activity, by applying "one-pot" reaction with the construction of stereogenic centers by organocatalyzed asymmetric Michael reactions.



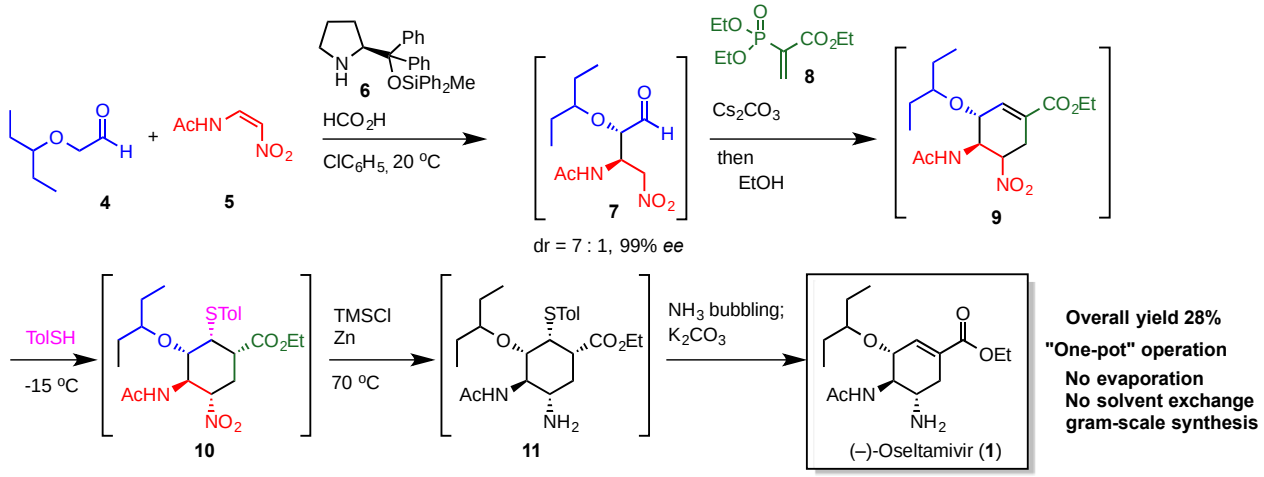
(–)-Oseltamivir (**1**) (–)-Horsfiline (**2**) (–)-Coerulescine (**3**)

Figure 1. (–)-Oseltamivir (**1**), (–)-Horsfiline (**2**), and (–)-Coerulescine (**3**)

Chapter 2. One-pot synthesis of (–)-Oseltamivir, "three-pot" synthesis of spirooxyindole alkaloids, and mechanistic investigation of organocatalyzed Michael addition of aldehydes into nitroalkens

(–)-Oseltamivir (**1**) is one of the most effective drugs for the treatment of influenza. It is important to develop robust and efficient preparation methods to produce sufficient quantities of **1** for worldwide use. On the other hand, "one-pot" reaction is practical approaches to conduct several transformations in a single vessel. It cuts several purification operations, and minimizes chemical wastes, enabling a shorter total production time.

I have developed a "one-pot" synthesis of (–)-Oseltamivir without any evaporation and solvent exchange on gram scale (Scheme 1).[6] Key reaction was the asymmetric Michael reaction of α-alkoxyaldehyde **4** with *cis*-alkene **5**, catalyzed by diphenylprolonol silyl ether **6**, to afford Michael adduct **7** in excellent yield and stereoselectivity. I discovered the choice of solvent and acid is important to achieve excellent yield and stereoselectivity. Michael reaction of **7** with phosphonate **8**, followed by intramolecular Horner-Wadsworth-Emmons reaction afforded cyclohexene **9**. The addition of toluenethiol furnished cyclohexane **10** with the desired configuration. Reduction of nitrogroup, and removal of toluenethiol afforded (–)-Oseltamivir (**1**). I successfully performed all reactions in the same reaction vessel without evaporation and solvent exchange on gram scale. The advantage of this synthesis is easy manipulation as all I have to do was just adding all reagents into the same reaction vessel sequentially. As a result, production time, cost, and chemical wastes were reduced. I have achieved the synthesis of (–)-Oseltamivir in only "one-pot" without evaporation and solvent exchange on gram scale.



Scheme 1. "One-pot" synthesis of (–)-Oseltamivir (**1**)

A key reaction was the Michael reaction of α-alkoxyaldehyde **4** and *cis*-nitroalkene **5**, catalyzed by **6**. I have discovered new mechanistic insights of this reaction (Figure 2). The discovery is as follows; 1) α-alkoxyaldehyde **4** generates both *E* and *Z*-enamines while aliphatic aldehyde generates only *E*-enamine, 2) *E* and *Z*-enamines are in equilibrium and acid accelerates isomerization, 3) *E*-enamine reacts faster with *trans*-nitroalkene **12** while *Z*-enamine reacts faster with *cis*-nitroalkene **5**. All of them contribute to the generation of 2*S*-isomer. The transition state models for *cis*-nitroalkene **5** (**TS-3** and **TS-4**) were proposed by determining the absolute configuration of the minor isomer of Michael product **7**-minor and by studying the Michael reaction of α-alkoxyaldehyde **4** with other *cis*-alkene Michael acceptors that cannot isomerize in geometry (i.e., with phenylmaleimide and naphthoquinone). The mechanistic study indicates that the Michael reaction can be effectively carried out by the correct orchestration of three reaction processes: 1) the speed of generation of the *E*/*Z*-enamines from **4** and **6**, 2) the relative reactivity of *E*- and *Z*-enamines toward the Michael acceptor **5** and **12**, and 3) the acid-promoted isomerization between the *E*- and *Z*-enamines.

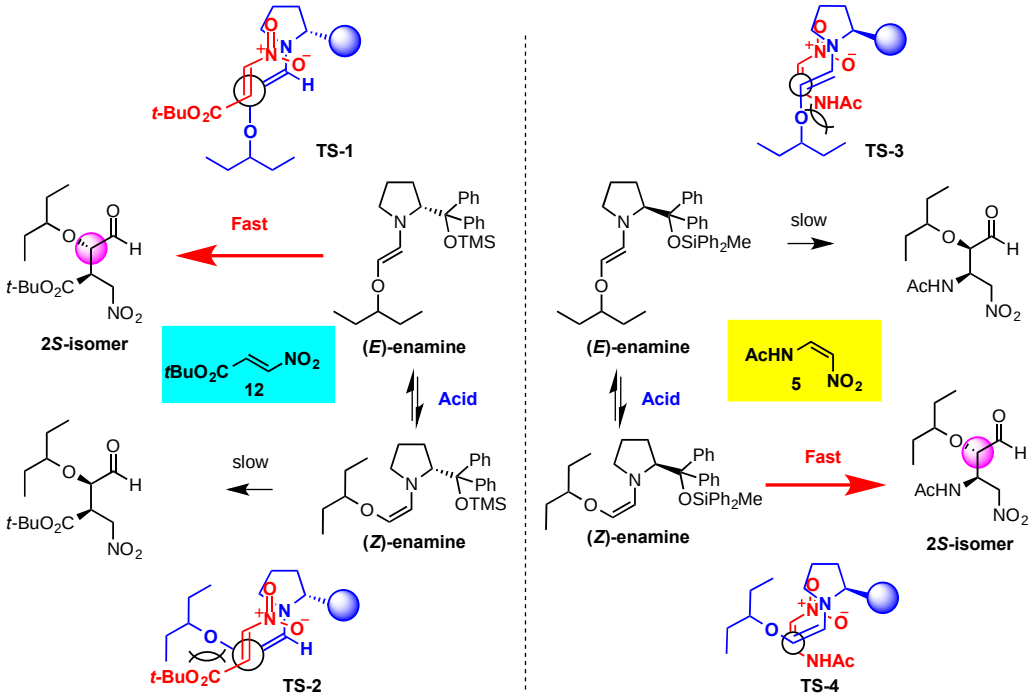
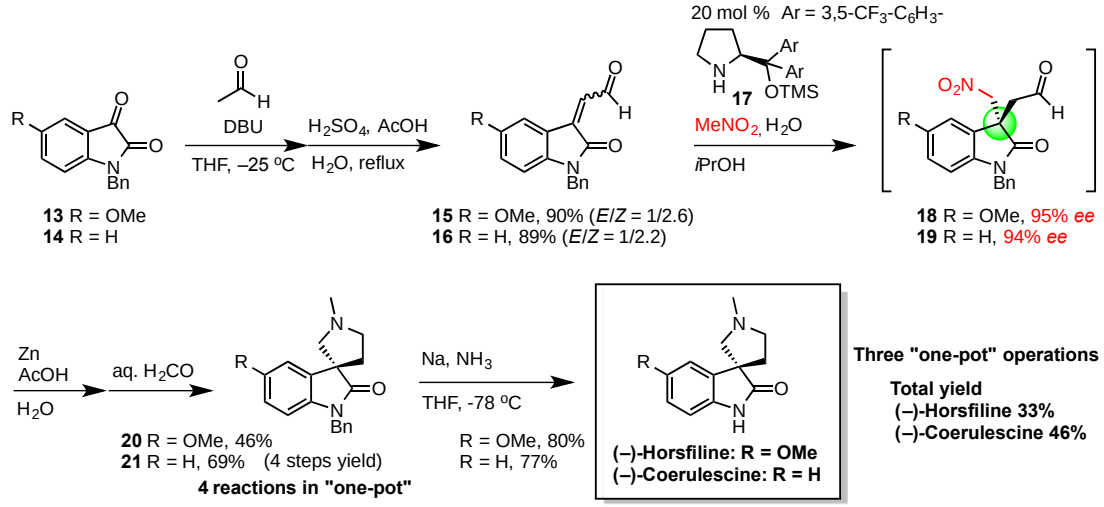


Figure 2. Mechanistic insights into organocatalyzed Michael reaction

Chapter 3. Asymmetric Michael addition of nitromethane to 2-oxoindoline-3-ylidene acetaldehyde and three "one-pot" sequential synthesis of (–)-Horsfiline and (–)-Coerulescine

The concept of "one-pot" was extended to the synthesis of spirooxyindole alkaloids, (–)-Horsfiline and (–)-Coerulescine. The spirooxyindole alkaloids show a variety of biological activity. Therefore, spirooxyindole derivatives have become attractive targets for drug discovery.[7] We aimed to develop an efficient synthesis of (–)-Horsfiline and (–)-Coerulescine. The main challenge was to construct the all-carbon quaternary stereogenic centers in a catalytic enantioselective fashion. I have achieved three "one-pot" sequential synthesis of (–)-Horsfiline and (–)-Coerulescine (Scheme 2).[8] The first reaction was the straightforward synthesis of 2-oxoindoline-3-ylidene acetaldehyde **15** or **16** from an isatin derivative **13** or **14** with acetaldehyde. I have developed asymmetric Michael reaction of nitromethane to **15** or **16** to construct the quaternary carbon center in excellent enantioselectivity. Reduction of nitro group, intra- and intermolecular reductive amination were conducted in the same reaction vessel to afford spirooxyindole **20** or **21**. Removal of protecting group afforded (–)-Horsfiline and (–)-Coerulescine.[4] Hence, three "one-pot" sequential syntheses of (–)-Horsfiline and (–)-Coerulescine were developed in good total yield.



Scheme 2. Three "one-pot" sequential synthesis of (–)-Horsfiline and (–)-Coerulescine

It should be noted that excellent enantioselectivity was observed even though mixture of *E*/*Z* isomer of **15** or **16** was used in the Michael reaction. I have demonstrated that isomerization exists between *E* and *Z*-isomer. The postulated course of enantioselectivity is shown in figure 3. Both *Z* and *E* isomer forms iminium ion ***Z*-22** or ***E*-22**, and isomerization would occur through the addition and elimination process of hydroxyl ion. Nitormethane reacts faster with ***Z*-22** considering the **TS-5** and **TS-6**, which has a steric repulsion between nitrogroup and aromatic ring. As a result, major enantiomer would be generated.

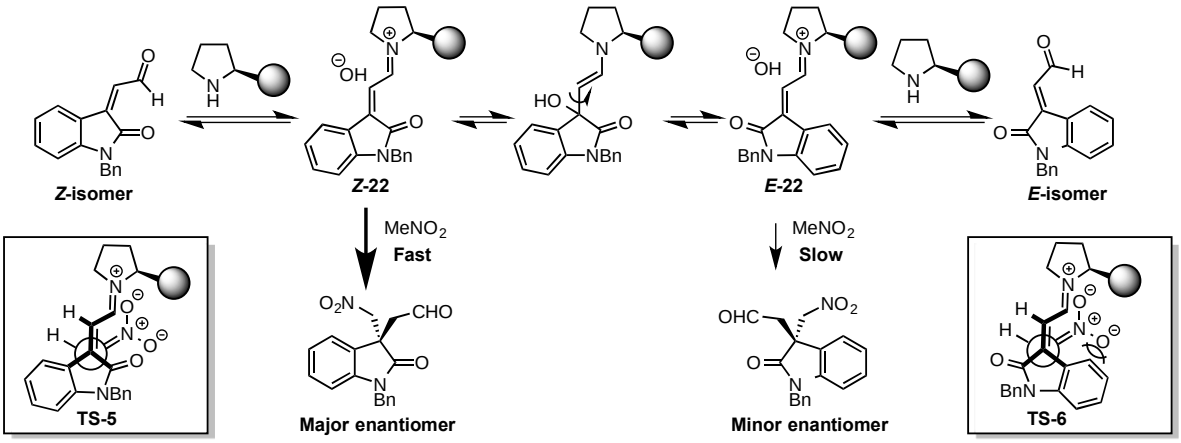
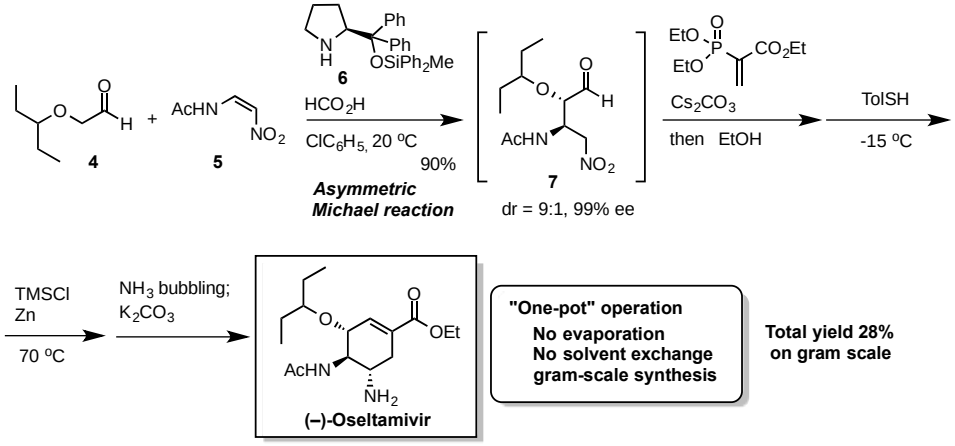


Figure 3. The course of excellent enantioselectivity

Chapter 4. Conclusion

The "pot-economy" synthesis of (–)-Oseltamivir, (–)-Horsfiline, and (–)-Coerulescine was described in this doctoral thesis. I have developed a "one-pot" synthesis of (–)-Oseltamivir and three "one-pot" sequential synthesis of (–)-Horsfiline and (–)-Coerulescine.

In chapter 2, a completely "one-pot" sequential synthesis of (–)-Oseltamivir without solvent evaporations or exchange on gram-scale was described (Scheme 3). Key reaction was the asymmetric Michael reaction of α-alkoxyaldehyde with *cis*-nitroalkene, catalyzed by diphenylprolinol silyl ether, to afford the Michael product in good yield with excellent diastereo- and enantio-selectivities. The mechanistic study of the Michael reaction revealed the course of stereoselectivity.



Scheme 3. Summary of "one-pot" synthesis of (–)-Oseltamivir

The three "one-pot" sequential synthesis of both (–)-Horsfiline and (–)-Coerulescine was described in chapter 3 (Figure 4). The first key reaction is the straightforward synthesis of 2-oxoindoline-3-ylidene acetaldehyde from an isatin derivative with acetaldehyde (eq. 1). The second key reaction was the construction of the all-carbon quaternary stereogenic centers (eq. 2). The Michael addition of nitromethane to 2-oxoindoline-3-ylidene acetaldehyde, by careful choice of diarylprolinol silyl ether catalyst and the reaction solvent, constructed the all-carbon quaternary stereogenic centers in excellent enantioselectivity. Hence, three "one-pot" sequential syntheses of (–)-Horsfiline and (–)-Coerulescine were developed in good total yield.

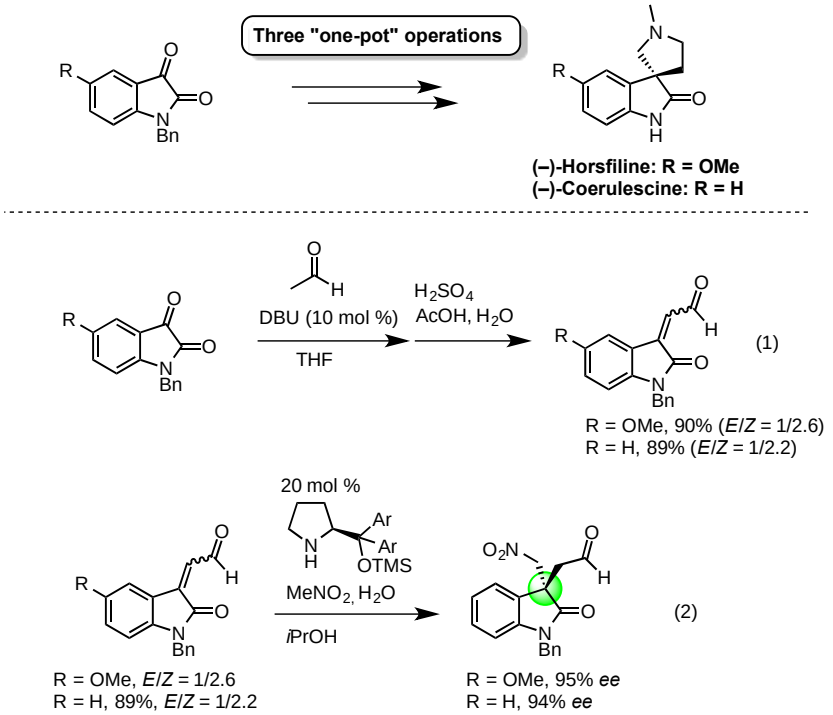


Figure 4, Summary of three "one-pot" sequential synthesis of (–)-Horsfiline and (–)-Coerulescine

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